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UNITED STATES DISTRICT COURT  
NORTHERN DISTRICT OF CALIFORNIA

IN RE: BEXTRA AND CELEBREX  
MARKETING SALES PRACTICES AND  
PRODUCT LIABILITY LITIGATION

CASE NO. M:05-CV-01699-CRB  
MDL No. 1699

This Order Relates to:  
  
ALL CASES

**MEMORANDUM AND ORDER RE:  
MOTIONS TO EXCLUDE EXPERT  
TESTIMONY**

In this Multi-District Litigation (“MDL”) proceeding, over 3000 plaintiffs allege that they or their loved ones suffered a heart attack, stroke or other adverse cardiovascular event as a result of taking Celebrex, a pain medication manufactured by defendant Pfizer, Inc. (“Pfizer”). Pfizer has moved to exclude any expert testimony to the effect that Celebrex is capable of causing a heart attack or stroke when ingested at 200 milligrams a day or 400 milligrams a day. Plaintiffs have also moved to exclude certain expert testimony offered by Pfizer. The Court held three days of hearings which included direct and cross examination of certain experts. After carefully considering the parties’ memoranda and evidence, and the testimony offered at the hearing, the Court concludes that plaintiffs have not presented scientifically reliable evidence that Celebrex causes heart attacks or strokes when ingested at the 200 milligram a day dose. In all other respects the parties’ motions are denied.

## BACKGROUND

Non-steroidal anti-inflammatory drugs (“NSAIDs”) have been widely used for pain relief for several years. NSAIDs, however, have certain side effects, including gastrointestinal toxicity which results in thousands of deaths every year. The pharmaceutical company Merck & Co., Inc. (“Merck”) developed Vioxx, and Pfizer (or, more precisely, its predecessors) developed Celebrex and Bextra, NSAIDs known as COX-2 inhibitors, with the expectation that they would have fewer gastrointestinal side effects than traditional NSAIDs. The Food and Drug Administration (“FDA”) approved Celebrex for adult arthritis in 1998, Vioxx in 1999, and Bextra in late 2001. The recommended dose of Celebrex was and is 200 milligrams a day (“mg/d”) for arthritis and 400 mg/d for rheumatoid arthritis.

In 2000 the results of a long-term randomized study of Celebrex known as CLASS (“Celecoxib Long-Term Arthritis Safety Study”) were published. The study was designed to evaluate the gastrointestinal side effects of taking Celebrex at 800 mg/d. Based on investigator reported cardiovascular events, the study showed no increased risk of heart attack or stroke by taking Celebrex over diclofenac or ibuprofen. Around the same time, a similar study of Vioxx, known as VIGOR, showed a four-fold increase in cardiovascular (“cv”) risk for patients taking Vioxx versus Aleve (naproxen). The FDA subsequently revised the labels of Celebrex and Vioxx to reflect the cv risk results of these studies.

Another Vioxx randomized clinical study, known as APPROVe, was published in 2004. This study demonstrated a two-fold increased risk of cv adverse events for patients taking Vioxx versus a placebo. This study contributed to Merck’s voluntary removal of Vioxx from the market on September 30, 2004.

The preliminary results of APC, a randomized, placebo-controlled study of Celebrex at 200 mg twice daily (400 mg/d) and 400 mg twice daily (800 mg/d) to evaluate whether Celebrex prevents the development of colon polyps, became available in late 2004. APC showed dose-related increased cv risk for patients taking Celebrex compared to placebo: more than doubling the risk for 200 mg twice daily and tripling the risk for

1 400 mg twice daily. The APC steering committee discontinued the study in December  
2 2004 because of these preliminary results.

3 In February 2005 the FDA convened an Advisory Committee to review the data on  
4 cv risk and NSAIDs, including COX-2 inhibitors. The Committee concluded that all  
5 COX-2 inhibitors increase cv risk versus placebo, but it did not make any findings as to  
6 what dose is required to increase the risk. It also concluded that the data was insufficient  
7 to determine if traditional NSAIDs also increase cv risk. With respect to Celebrex, the  
8 FDA found that APC is the “strongest data in support of an increased risk of serious  
9 adverse CV events.” FDA Decision Memorandum, April 6, 2005, at 4, Declaration of  
10 Loren Brown (“Brown Decl.”) Exh. 16. The FDA also noted that APC’s results had not  
11 been replicated by preliminary data from two other randomized controlled clinical studies:  
12 (1) PreSAP, a colon polyp prevention trial of Celebrex at 400 mg/d; and (2) ADAPT, an  
13 Alzheimer’s trial of Celebrex at 200 twice daily (400 mg/d). Both studies showed no  
14 increased cv risk for Celebrex versus placebo.

15 The FDA subsequently asked Pfizer to remove Bextra from the market, which  
16 Pfizer did in April 2005. The FDA also determined that the benefits of Celebrex outweigh  
17 its risks and therefore it allowed Celebrex to remain on the market. Celebrex is the only  
18 COX-2 inhibitor currently on the market.

19 The FDA also directed all NSAIDs, including Celebrex, to include a black box  
20 warning on their labels. The black box warns of cv risk as follows:

21 **Cardiovascular Risk**

- 22 • CELEBREX may cause an increased risk of serious cardiovascular  
23 thrombotic events, myocardial infarction, and stroke, which can be fatal.  
24 All NSAIDs may have a similar risk. This risk may increase with duration  
of use. Patients with cardiovascular disease or risk factors for  
cardiovascular disease may be at greater risk . . . .

25 Celebrex 2007 Label, Brown Decl. Exh. 3.

26 As a result of these developments, thousands of patients and patient representatives  
27 filed lawsuits against Merck and Pfizer alleging that the patient had suffered a serious  
28

1 cardiovascular injury, such as a heart attack or stroke, due to their ingestion of Vioxx,  
2 and/or Celebrex and/or Bextra. All of the federal court claims against Merck were  
3 consolidated in a MDL action in New Orleans. All of the federal court claims against  
4 Pfizer were consolidated into this MDL proceeding.

### 5 **THE DAUBERT MOTIONS**

6 Pursuant to Federal Rule of Evidence 702, Pfizer moves to exclude plaintiffs'  
7 experts from offering the following six opinions:

- 8 1. That 200 mg/d of Celebrex causes heart attacks and strokes;
- 9 2. That 400 mg/d of Celebrex causes heart attacks and strokes;
- 10 3. That Celebrex causes heart attacks or strokes more than three days after a  
11 patient stops taking it;
- 12 4. That Celebrex causes strokes; and;
- 13 5. That Celebrex causes heart attacks or strokes at durations of less than 33  
14 months of continuous daily use.

15 Pfizer also asks the Court to exclude any expert opinion that Celebrex caused any  
16 individual plaintiff's heart or stroke absent epidemiology evidence that demonstrates a  
17 relative risk greater than 2.0, that is, that Celebrex doubles the risk. Plaintiffs have moved  
18 to exclude certain expert testimony offered by Pfizer; specifically, they seek to exclude  
19 admission of the meta-analyses performed by plaintiffs' experts.

20 In connection with these motions, the parties submitted direct written testimony of  
21 their respective experts as well as legal memoranda. The Court then held three days of  
22 hearings, which were conducted jointly with the New York Justice presiding over the New  
23 York State Celebrex and Bextra cases. Plaintiffs' experts Dr. Neil Doherty, Dr. Joel  
24 Bennett, Dr. Nicholas Jewell and Dr. Maryilyn Rymer testified on direct and cross-  
25 examination, along with defendant's expert Dr. Milton Packer. The parties also submitted  
26 post-hearing memoranda. The motions are now ripe for decision.

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## LEGAL STANDARD

### A. Admissibility of Expert Testimony

When evaluating the admissibility of expert testimony, the trial judge “must engage in a difficult, two-part analysis.” Daubert v. Merrill Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1315 (9th Cir. 1995) (Daubert II). First, the court must “determine nothing less than whether the experts’ testimony reflects ‘scientific knowledge,’ whether their findings are ‘derived by the scientific method,’ and whether their work product amounts to ‘good science.’” Id. (quoting Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 589-90, 593 (1993)); see also In Re Silicone Gel Breast Impl. Prod. Liab. Lit., 318 F.Supp.2d 879, 890 (C.D. Cal. 2004) (“[T]he trial judge in all cases of proffered expert testimony must find that it is properly grounded, well-reasoned, and not speculative before it can be admitted.”) (quoting Fed. R. Evid. 702 Advisory Committee’s Notes). The trial judge’s obligation “is to make certain that an expert . . . employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.” Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152 (1999).

Many factors may be relevant to the reliability inquiry, including: (1) whether the proffered theory or technique has been tested, (2) whether the theory or technique has been subjected to peer review and publication, (3) the known or potential rate of error of the technique or theory when applied, and (4) the “general acceptance” of the theory or technique in the scientific community. Daubert, 509 U.S. at 593-94.

[C]ourts have also found the following factors relevant in assessing the reliability of expert testimony: (1) whether the expert is proposing to testify about matters growing directly out of independent research he or she has conducted or whether the opinion was developed expressly for purposes of testifying; (2) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion; (3) whether the expert has adequately accounted for obvious alternative explanations; (4) whether the expert is being as careful as he would be in his regular professional work; and (5) whether the field of expertise claimed by the expert is known to reach reliable results for the type of opinion offered.

1 In Re Silicone Gel Breast Impl. Prod. Liab. Lit., 318 F.Supp.2d at 890 (citing  
2 Fed.R.Evid. 702 Advisory Committee’s Notes).

3 In addition to determining reliability, the court “must ensure that the proposed  
4 expert testimony is ‘relevant to the task at hand,’ i.e., that it logically advances a material  
5 aspect of the proposing party’s case.” Daubert II, 43 F.3d at 1315 (quoting Daubert, 509  
6 U.S. at 597). This is known as the “fit” requirement. Id. Here, the pertinent fit inquiry is  
7 “causation.” The parties’ motions address expert testimony on the causation inquiry.

#### 8 **B. Causation**

9 Causation in toxic tort or pharmaceutical personal injury cases “is typically  
10 discussed in terms of generic and specific causation.” In Re Hanford Nuclear Reservation  
11 Lit., 292 F.3d 1124, 1133 (9th Cir. 2002). General or generic causation means “whether  
12 the substance at issue had the capacity to cause the harm alleged.” Id. In Hanford, for  
13 example, the Ninth Circuit explained that the general causation inquiry was “whether  
14 exposure to a substance for which a defendant is responsible, such as radiation at the level  
15 of exposure alleged by plaintiffs, is capable of causing a particular injury or condition in  
16 the general population.” Id.

17 To ultimately prevail in such a lawsuit, however, a plaintiff must show both  
18 general and “individual” or “specific” causation. Id. Specific causation refers to whether  
19 a particular individual suffers from a particular ailment as a result of exposure to a  
20 substance. Id. That is, that the challenged conduct, here, the taking of Celebrex at a  
21 certain dose for a particular amount of time, was “the cause-in-fact” of the particular  
22 plaintiff’s injury. Id.

23 The parties’ motions involve the use of epidemiology to prove causation. “The  
24 field of epidemiology addresses the incidence, distribution and etiology (causation) of  
25 disease in human populations by comparing individuals exposed to a particular agent to  
26 unexposed individuals to determine whether exposure increases the risk of disease.” In  
27 Re Silicone Gel Breast Implant Prod. Liab. Lit., 318 F.Supp.2d at 892. Scientists use  
28 “relative risk” to identify an association between, for example, the ingestion of a drug and

1 a disease.

2 For example, if a study found that 10 out of 1000 women with breast implants were  
3 diagnosed with breast cancer and 5 out of 1000 women without implants (the  
4 “control” group) were diagnosed with breast cancer, the relative risk of implants is  
5 2.0, or twice as great as the risk of breast cancer without implants. This is so,  
6 because the proportion of women in the implant group with breast cancer is 0.1  
(10/1000) and the proportion of women in the non-implant group with breast  
cancer is 0.05 (5/1000). And 0.1 divided by 0.05 is 2.0.

7 Id. A relative risk of 1.0 suggests that there is no association between the product and the  
8 disease, that is, the same numbers of people using the product are diagnosed with the  
9 disease as those not using the product. Similarly, a relative risk of less than 1.0 suggests  
10 that the product is actually “protective” of the disease: fewer people using the product  
11 contract the disease than those not taking the product. Id. at n.5.

12 In general, epidemiology studies are probative of general causation: a relative risk  
13 greater than 1.0 means the product has the capacity to cause the disease. “Where the  
14 study properly accounts for potential confounding factors and concludes that exposure to  
15 the agent is what increases the probability of contracting the disease, the study has  
16 demonstrated *general* causation—that exposure to the agent is capable of causing [the  
17 illness at issue] in the general population.” Id. at 893 (internal quotation marks and  
18 citation omitted).

19 Such studies can also be probative of specific causation, but only if the relative risk  
20 is greater than 2.0, that is, the product more than doubles the risk of getting the disease.

21 When the relative risk is 2.0, the alleged cause is responsible for an equal  
22 number of cases of the disease as all other background causes present in the  
23 control group. Thus, a relative risk of 2.0 implies a 50% probability that the  
24 agent at issue was responsible for a particular individual’s disease. This  
25 means that a relative risk that is greater than 2.0 permits the conclusion that  
the agent was more likely than not responsible for a particular individual’s  
disease.

26 Id. at 893. The issue on these motions, however, is not specific causation; there is  
27 no particular plaintiff before the Court. Rather, the primary issue is whether the  
28 Court should permit plaintiffs’ experts to testify that Celebrex is capable of causing

1 heart attacks or strokes at certain doses.

## 2 **EPIDEMIOLOGY STUDIES AND TERMS**

3 Before discussing the parties' motions, it is important to identify the different  
4 epidemiology studies relied upon by the experts. There are generally three types of  
5 clinical epidemiology studies at issue on the parties' motions: (1) randomized controlled  
6 clinical trials, (2) observational studies, and (3) meta-analyses.

7 The "gold standard" for determining whether a drug is related to the risk of  
8 developing an adverse health outcome is a "randomized clinical trial" in which the  
9 subjects are randomly assigned to one of two groups: one group exposed to the drug of  
10 interest and the other not exposed. After a period of time the study participants in both  
11 groups are evaluated for an adverse health outcome. Federal Judicial Center, Reference  
12 Manual on Scientific Evidence 338 (2d ed. 2000). "Randomization minimizes the  
13 likelihood that there are differences in relevant characteristics between those exposed to  
14 the agent and those not exposed," such as smoking, obesity, aspirin use and so on that  
15 could account for any difference in outcomes between the two groups. Id.

16 An "observational study" evaluates causation by comparing the risk of disease  
17 between patients exposed to a given substance and patients who were not exposed. The  
18 study may be prospective, identifying patients and then following them for a period of  
19 time, or retrospective, identifying patients and then performing a medical chart review to  
20 determine what happened during the period they did or did not take the drug. The  
21 downside to observational studies is that because the investigators do not control who  
22 participates in the study, it is more difficult to control for confounding factors such as  
23 smoking, obesity and the like. The investigator attempts to address the possible role of  
24 confounding factors "by considering them in the design of the study and in the analysis  
25 and interpretation of the study results." Id. at 339.

26 There are two types of observational studies: a cohort study and a case control  
27 study. A cohort study identifies patients who are taking the drug (exposed) and follows  
28 them for a certain amount of time to determine if they have the alleged bad outcome, here,



1 such outcome is heart attack or stroke. The cohort study also identifies people not taking  
2 the drug and follows them (unexposed). The study then compares the rate of the alleged  
3 bad outcomes in group one with the rate in group two to compute the “relative risk.” Id.  
4 at 339-40.

5 A case control study identifies persons who had a bad outcome (the cases), for  
6 example, patients in the United Kingdom database that had a heart attack within the last  
7 three years, and reviews their medical records to determine how many of those persons  
8 were taking the studied drug around the time of their heart attack. The study then  
9 identifies an equal number of people who did not have a heart attack (the controls) and  
10 determines how many of them were taking the drug. Id. From those figures an “odds  
11 ratio” is computed. For example, if the percentage of people taking Celebrex in both  
12 groups is the same, the odds ratio is 1.0; that is, taking Celebrex did not increase the risk  
13 of heart attack.

14 Sometimes randomized controlled studies and observational studies of the same  
15 drug will have conflicting results; some will show a statistically significant association  
16 while others will not. A meta-analysis pools the results of various studies to arrive at a  
17 single figure to represent the totality of the studies reviewed. “In a meta-analysis, studies  
18 are given different weights in proportion to the sizes of their study populations and other  
19 characteristics.” Id. at 380. Meta-analysis has the advantage of pooling more data so that  
20 the results are less likely to be misleading solely due to chance. On the other hand, one  
21 problem with meta-analysis, particularly in meta-analysis of observational studies, is that  
22 the pooled studies often use disparate methodologies.

23 When reviewing the results of a study, whether it is a randomized clinical trial,  
24 observational trial, or a meta-analysis of such trials, it is important to consider the  
25 confidence interval. The confidence interval is, in simple terms, the “margin of error.”  
26 So, for example, if a given study showed a relative risk of 1.40 (a 40 percent increased  
27 risk of adverse events), but the 95 percent confidence interval is .8 to 1.9, we would say  
28 that we are 95 percent confident that the true value, that is, the actual relative risk, is

1 between .8 and 1.9. Because the confidence interval includes results which do not show  
2 any increased risk, and indeed, show a decreased risk, that is, it includes values less than  
3 1.0, we would say the study does not demonstrate a “statistically significant” increased  
4 risk of an adverse outcome. Confidence intervals are calculated, in part, based on the  
5 number of people and events included in the study. “The larger the sample size in a study  
6 (all other things being equal), the narrower the confidence boundaries will be (indicating  
7 greater statistical stability), thereby reflecting the decreased likelihood that the association  
8 found in the study would occur if the true association is 1.0 [no increased or decreased  
9 risk].” Id. at 361.

10 With these terms in mind, the Court now turns to the parties’ motions.

## 11 **DISCUSSION**

### 12 **I. Pfizer’s Motion**

13 A threshold question raised by Pfizer’s motion is whether a particular dose of  
14 Celebrex is relevant to the general causation inquiry. Pfizer seeks to exclude any opinion  
15 that Celebrex is capable of causing heart attacks and strokes at 200 mg/d as well as any  
16 opinion that Celebrex is capable of causing heart attacks and strokes at 400 mg/d. It does  
17 not move to exclude expert testimony that Celebrex is capable of causing heart attacks and  
18 strokes when a patient ingests 800 mg/d, at least when taken over many months. Thus,  
19 Pfizer’s motion assumes that Celebrex at different doses can have different cardiovascular  
20 effects.

21 The Court finds that dose matters. All of plaintiffs’ experts, with perhaps a single  
22 exception, agree that there is a dose effect with Celebrex; that is, that it is more toxic, and  
23 is therefore more likely to cause an adverse side effect, when taken at greater doses. See  
24 Reference Manual on Scientific Evidence at 403 (“There are three central tenets of  
25 toxicology. First, ‘the dose makes the poison’; this implies that all chemical agents are  
26 intrinsically hazardous--whether they cause harm is only a question of dose. Even water,  
27 if consumed in large quantities, can be toxic.”); see also Mitchell v. Gencorp, 165 F.3d  
28 778, 781 (10th Cir. 1999) (noting that to prevail in a toxic tort case a “a plaintiff must

1 demonstrate ‘the levels of exposure that are hazardous to human beings generally as well  
2 as the plaintiff’s actual level of exposure to the defendant’s toxic substance before he or  
3 she may recover”) (internal quotation marks and citation omitted); Allen v. Penn. Eng’g  
4 Corp., 102 F.3d 194, 199 (5th Cir. 1996) (explaining that in toxic tort cases, “[s]cientific  
5 knowledge of the harmful level of exposure to a chemical plus knowledge that plaintiff  
6 was exposed to such quantities are minimal facts necessary to sustain the plaintiff’s  
7 burden”); see also Hanford Nuclear Reservation Lit., 292 F.3d at 1133 (explaining that  
8 the general causation inquiry is whether exposure to the challenged substance “*at the level*  
9 *of exposure alleged by the plaintiffs*” is capable of causing the alleged injuries”)  
10 (emphasis added). As plaintiffs’ cardiology expert, Dr. Neil Doherty, testified: it is a  
11 “fundamental principal of medicine” and “medical causality” that the risk of adverse  
12 cardiovascular events with Celebrex is dose-related. Transcript of October 10, 2007  
13 Hearing (“Oct. 10 TR”) at 328. Thus, the Court must analyze plaintiffs’ experts’ opinions  
14 as to causation at 200 mg/d separate from their opinions as to 400 mg/d.

15 **A. 200 mg/d**

16 Celebrex at 200 mg/d and the risk of adverse cv events has not been studied in  
17 published, large, long-term randomized controlled trials. Nonetheless, included in the  
18 record are approximately 30 unpublished randomized controlled trials, albeit of short  
19 duration and small size. These studies do not demonstrate any association between  
20 Celebrex and adverse cv outcomes. A meta-analysis of all available published and  
21 unpublished randomized clinical trials of all COX-2 inhibitors as well as traditional  
22 NSAIDs found that while COX-2 inhibitors as a whole are associated with a moderate  
23 increase in the risk of adverse cv events, no such association is found with the available  
24 data for Celebrex at 200 mg/d or less.<sup>1</sup>

25 The record also includes observational studies with Celebrex data, mostly at 200

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27 <sup>1</sup> Patricia Kearney, et al., Do selective cyclooxygenase-2 inhibitors and traditional non-  
28 steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of  
randomized trials, British Medical Journal 2006, June 3; 332(7553): 1302-8.

1 mg/d. These observational studies together include more than 8,000 adverse cv events,  
2 and all of the studies with the most events demonstrate no statistically significant  
3 association between Celebrex at 200 mg/d and adverse cv events. A meta-analysis  
4 performed by an independent researcher unaffiliated with Pfizer (“McGettigan”)  
5 concluded that while Vioxx does increase the risk of adverse cv events, “[i]n doses of  
6 around 200 mg/d, [Celebrex] was not associated with an increased risk . . . .”<sup>2</sup> Another  
7 meta-analysis of eight observational studies showed no increased risk from Celebrex 200  
8 mg/d compared to patients taking no medication.<sup>3</sup>

9 In sum, there are no randomized controlled trials or meta-analyses of such trials or  
10 meta-analyses of observational studies that find an association between Celebrex 200  
11 mg/d and a risk of heart attack or stroke. And most observational studies, indeed, the  
12 observational studies that include 97 percent of the reported adverse cv events, also find  
13 no statistically significant association. It is thus unsurprising that most of plaintiffs’  
14 experts agree that the available evidence at 200 mg/d is inadequate to prove causation.  
15 See Deposition Testimony of Dr. Joel Bennett at p. 537, Brown Reply Decl. Exh. 108 (“I  
16 think that if you look at all the evidence, I think at 200 milligrams it’s hard to make a case  
17 that Celebrex has toxicity. It doesn’t mean that, again, that in individual cases it couldn’t,  
18 it could be lost in the big scheme of things, but, in fact, the data don’t suggest that in a  
19 large population it increases the risk.”); Deposition Testimony of Dr. Lemue Moyer at  
20 p. 268, Brown Reply Decl. Exh. 109 (“[T]here’s no study that convincingly demonstrates  
21 a signal of cardiovascular events at very low doses such as 200 per day.”); Deposition  
22 Testimony of Dr. Nicholas Jewell at p. 130, Brown Reply Decl. Exh. 110 (when asked  
23 whether there is reliable scientific evidence to establish that 200 mg/d causes heart attacks  
24 and strokes he responded that the evidence is not sufficient “to be definitive”); Deposition

25 <sup>2</sup> Patricia McGettigan, et al., Cardiovascular Risk and Inhibition of Cyclooxygenase: A  
26 Systematic Review of the Observational Studies of Selective and Nonselective inhibitors  
of Cyclooxygenase 2, JAMA 2006 Oct 4; 296(13): 633-44.

27 <sup>3</sup> S. Hernandez-Diaz et al., Non-steroidal anti-inflammatory drugs and the risk of acute  
28 myocardial infarction, Basic Clin. Pharmacol. Toxicol. 2006 Mar; 98(3):266-274, at 270,  
273.

1 of Dr. James M. Wright at pp. 83-84, 92, Brown Decl. Reply Exh. 106 (stating that it has  
2 not been proven that at 200 mg/d Celebrex increases the risk of heart attack because “we  
3 don’t have enough information”).

#### 4 **1. Dr. Neil Doherty**

5 Plaintiffs’ cardiology expert, Dr. Neil Doherty, nonetheless asserts “to a reasonable  
6 degree of medical probability that the 200 mg dose of Celebrex can increase the risk of  
7 MI’s [heart attacks].” Written Direct Examination of Dr. Neil F. Doherty III (“Doherty  
8 Written Direct”) at ¶ 18. He reaches his opinion by first identifying his conclusion—  
9 causation at 200 mg/d—and then cherry-picking observational studies that support his  
10 conclusion and rejecting or ignoring the great weight of the evidence that contradicts his  
11 conclusion. Dr. Doherty’s opinion does not reflect scientific knowledge, is not derived by  
12 the scientific method, and is not “good science;” it is therefore inadmissible.

13 First, Dr. Doherty is not qualified to favor certain observational studies over the  
14 great weight of the epidemiologic evidence to give an opinion on causation. He is a  
15 clinical cardiologist who sees patients 95 percent of his physician time. He does not have  
16 any specialized epidemiology training. He has not published any research since 1992, and  
17 his 13 publications are unrelated to the subject matter of these lawsuits. He has never  
18 participated in an observational study of any kind. He is therefore not qualified to opine  
19 that one or two observational studies are correct while all the other studies (the studies  
20 that include 97 percent of the adverse cv events) are wrong. Moreover, he only became  
21 interested in Celebrex and cv risk *after* he was retained by plaintiffs in this litigation;  
22 indeed, although the issue of COX-2 inhibitors and adverse cv events has been well  
23 known since at least 2005, he did not discontinue prescribing Celebrex until after  
24 plaintiffs retained him as an expert in this case. Doherty Written Direct at ¶ 2. Dr.  
25 Doherty’s opinion was developed for the purpose of this litigation. See Daubert II, 43  
26 F.3d at 1317 (“One very significant fact to be considered is whether the experts are  
27 proposing to testify about matters growing naturally and directly out of research they have  
28 conducted independent of the litigation, or whether they have developed their opinions

1 expressly for purposes of testifying.”).

2 Second, apart from his lack of relevant experience and training (or because of it),  
3 the foundation of his opinion--wholly rejecting the McGettigan meta-analysis and the  
4 other observational studies that do not support his opinion--is not a scientifically valid  
5 methodology. For example, while he justifies his wholesale rejection of McGettigan on  
6 the blanket ground that meta-analysis is inappropriate for observational studies, plaintiffs’  
7 other experts rely on such studies; indeed, Dr. Bennett testified that McGettigan is a “good  
8 study.” Dr. Bennett Depo. at p. 187-88, Brown Reply Decl. Exh. 108. And the American  
9 Heart Association Committee that developed a “Science Advisory” on the use of NSAIDs  
10 also relied on McGettigan. Finally, Dr. Doherty testified that he prefers the Oxford  
11 Centre for Evidence Based Medicine ranking of the levels of evidence that a scientist  
12 should consider. Doherty Written Direct at ¶ 21-22. That ranking identifies systematic  
13 review, including meta-analysis, as the highest level for each category of evidence. Oct.  
14 10 TR at 350.

15 Third, Dr. Doherty testified that the “strongest evidence” for his 200 mg/d opinion  
16 “is the Andersohn study published in Circulation in 2006.”<sup>4</sup> Doherty Written Direct at  
17 ¶ 18. He attempts to justify his heavy reliance on Andersohn by asserting that it is the  
18 “best designed” of all the observational studies. When asked why, however, Dr. Doherty  
19 responded only that the study is derived from the United Kingdom database which is  
20 among the most complete in the world. Oct. 10 TR at 309-10. He also mentioned that  
21 Andersohn is a prospective, rather than retrospective study. Id. at 310. But many of the  
22 other studies he rejects out of hand are also prospective, and he does not cite anything in  
23 the medical literature that suggests that it is a valid scientific method to prefer one study  
24 over many that have contradictory results simply because the study that supports the  
25 expert’s conclusion utilized the United Kingdom database.

26 \_\_\_\_\_  
27 <sup>4</sup> Frank Andersohn, et al., Use of First-and Second-Generation Cyclooxygenase-2-  
28 Selective Nonsteroidal Anti-inflammatory Drugs and Risk of Acute Myocardial  
Infarction, Circulation, 2006 Apr 25; 113(16): 1950-7.

1 Fourth, Dr. Doherty's reliance on Andersohn as "the strongest evidence" of an  
2 increased risk at 200 mg/d is undermined by his own testimony that Andersohn's results  
3 do not make "biological sense." Oct. 10 TR at 363-64. Andersohn found the increased  
4 risk of heart attack was higher at shorter durations of use (less than three months) than at  
5 higher durations; indeed, there was no statistically significant association at durations  
6 greater than three months, a finding that directly contradicts Dr. Doherty's testimony that  
7 the risk of heart attack increases with duration of use. Oct. 10 TR at 359-61. Andersohn  
8 also found that the risk of heart attack is statistically significant in patients without cv risk  
9 factors, but is not statistically significant in patients with such risk factors. Id. at 364.  
10 Again, this finding directly contradicts Dr. Doherty's testimony that the risk of heart  
11 attack from Celebrex is greater in patients with heart disease. To conclude that Celebrex  
12 200 mg/d causes heart attacks and strokes based on a study that does not make "biological  
13 sense" is not sound science.

14 Fifth, Dr. Doherty's opinion is based on his fundamental misunderstanding of  
15 Andersohn. Dr. Doherty testified that Andersohn is a cohort study and he "puts a lot more  
16 weight" into cohort studies as opposed to case control studies. Oct. 10 TR at 255, 309,  
17 350. He repeatedly testified that he relies on Andersohn out of all of the available  
18 evidence because it is a good cohort study. See, e.g., id. at 313, 315. When he was  
19 confronted with Andersohn's own description of the study, however, Dr. Doherty  
20 conceded that Andersohn is not a cohort study, but is instead "a case-control study nested  
21 within a cohort study." Id. at 352.

22 Dr. Doherty also insisted that Andersohn used cox proportional hazard analysis, the  
23 analysis most commonly used for cohort studies. Oct. 10 TR at 320-21, 355. On cross-  
24 examination, however, he could not identify where in the study the authors disclose that  
25 they used cox-proportional hazard analysis and Dr. Doherty pointedly did not clarify his  
26 testimony on re-direct. The Court has reviewed Andersohn and it does not indicate that  
27 the study authors used cox-proportional hazard analysis; rather, they used logistic  
28 regression which resulted in an "odds ratio," an analysis consistent with case control

1 studies. Dr. Doherty's fundamental misunderstanding of the study he "relied most  
2 strongly on" to support his opinion, Doherty Written Direct at ¶ 31, is perhaps explained  
3 by his inability to explain the difference between a cohort study and case control study  
4 "off the top of his head," Oct. 10 TR at 348, and his inability to define the cox  
5 proportional hazards model or explain logistic regression analysis. Id. In any event, as  
6 Andersohn is a case control study, Dr. Doherty's heavy reliance upon it is unreliable in  
7 light of his own blanket rejection of all of the case control studies showing no association  
8 between Celebrex 200 mg/d and cv risk on the ground that case control studies are not as  
9 reliable as cohort studies. Doherty Written Direct at ¶ 37.

10 While Andersohn is the "strongest evidence" supporting Dr. Doherty's opinion, he  
11 also cited an additional observational study, Gislason.<sup>5</sup> Gislason, however, had few  
12 events and merely evaluated COX-2 inhibitors and the risk of a heart attack in patients  
13 who had already had a heart attack. Moreover, the study failed to control for smoking, a  
14 well-known risk for heart attack, as well as aspirin use, even though another of plaintiffs'  
15 experts, Dr. Maryilyn Rymer, criticized another observational study for not adjusting for  
16 aspirin use. Dr. Maryilyn Rymer Written Direct Testimony ("Rymer Written Direct") at  
17 ¶ 34. In light of these limitations, and the totality of the available evidence, Gislason does  
18 not salvage Dr. Doherty's opinion that Celebrex at 200 mg/d can cause heart attacks.

19 Dr. Doherty also relied on the "imbalance hypothesis" as evidence that it is  
20 biologically plausible that Celebrex causes heart attacks. This hypothesis asserts that  
21 COX-2 inhibitors as a class, that is, Vioxx, Bextra and Celebrex, create an imbalance in  
22 the arteries by blocking prostacyclin (an anti-clotting agent). Under this theory, the  
23 imbalance caused by ingesting a COX-2 will lead to an adverse cv event if the patient  
24 already has a risk factor, such as high blood pressure, smoking, or high cholesterol. Dr.  
25 Doherty argues that this hypothesis means that it makes sense that Celebrex increases the

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26 <sup>5</sup> Gunnar H. Gislason, et al., Risk of Death or Reincarnation Associated With the Use of  
27 Selective Cyclooxygenase-2 Inhibitors and Nonselective Nonsteroidal Antiinflammatory  
28 Drugs After Acute Myocardial Infarction, *Circulation*, 2006 June 27; 113(25): 2906-13.



1 risk of heart attacks and strokes. He did not explain, however, how he reconciles this  
2 theory with Andersohn—the strongest evidence of his causation opinion—which showed  
3 a greater risk of heart attacks in patients with no cv risk factors.

4 In any event, both Dr. Doherty and Dr. Joel Bennett—plaintiffs’ imbalance  
5 hypothesis expert—agree that the only way to prove the hypothesis is to look at the data  
6 from epidemiological studies. Oct. 10 TR at 373. For example, Dr. Bennett agreed that  
7 the only method available to determine how much Celebrex is needed (that is, what dose)  
8 to create an imbalance sufficient to cause a heart attack is patient studies. Oct. 9 TR at  
9 209, 210. As is explained above, the patient studies do not demonstrate an association  
10 between Celebrex 200 mg/d and heart attack or stroke; therefore, the imbalance  
11 hypothesis—even if true—(and it is only one of many possible explanations for the  
12 apparent increased risk of heart attacks from COX-2 inhibitors at certain doses) does not  
13 support Dr. Doherty’s opinion that Celebrex is capable of causing heart attacks at 200  
14 mg/d.

## 15 2. Dr. Maryilyn Rymer

16 Dr. Maryilyn Rymer’s testimony does not provide the missing link. Dr. Rymer is a  
17 neurologist and plaintiffs offered her as a stroke expert, essentially to opine that Celebrex  
18 causes strokes as well as heart attacks. In her written direct testimony she opines that “the  
19 totality of the scientifically reliable evidence supports that [Celebrex] can cause strokes  
20 and other cardiovascular events at all therapeutic doses, especially in those individuals  
21 who are high risk for cardiovascular events.” Rymer Written Direct at ¶ 7. She admits  
22 that there is no data from randomized controlled trials to support her conclusion at 200  
23 mg/d; instead, she primarily relies on (1) the imbalance hypothesis, (2) the same  
24 Andersohn study upon which Dr. Doherty relies, and (3) the Wellpoint data, an  
25 unpublished observational study of unknown design. In other words, Dr. Rymer, as does  
26 Dr. Doherty, ignores the vast majority of the evidence in favor of the few studies that  
27 support her conclusion.

28 The Court has already addressed the imbalance hypothesis and the Andersohn

1 study, neither of which provide scientifically valid support for her opinion in light of the  
2 great weight of the epidemiologic evidence. It is worth adding, however, that Dr.  
3 Rymer's reliance on the Andersohn heart attack study is inconsistent with her criticism of  
4 the Andersohn stroke study. The latter study, performed by the same Andersohn as the  
5 heart attack study, indeed, it is the same study but focused on stroke rather than heart  
6 attack outcomes, found no statistically significant increased risk of stroke associated with  
7 Celebrex use at 200 mg/d. Dr. Rymer criticized the stroke study for not controlling for  
8 aspirin use and having a 10 percent error rate; yet the Andersohn heart attack study suffers  
9 from the same limitations.

10 Dr. Rymer relies heavily on an unpublished, non-peer reviewed study from a  
11 managed care organization ("the Wellpoint Report"). Dr. Rymer attaches to her written  
12 direct testimony a letter from Wellpoint to the FDA summarizing the results of the study.  
13 The letter discloses a relative risk from Celebrex use of 1.19 when the data is analyzed to  
14 control for "age and other cardiovascular risk factors;" however, this very low risk  
15 includes *all* doses of Celebrex. Moreover, the letter does not identify study design, the  
16 analysis used, or even the confidence intervals. Dr. Rymer admitted on cross-examination  
17 that the study also fails to account for critical compounding factors such as smoking. This  
18 unpublished, unreviewed study, which combines all doses of Celebrex, and fails to adjust  
19 for critical compounding factors such as smoking, is not a scientifically valid basis for Dr.  
20 Rymer's rejection of all the other observational data--including meta-analyses--that do not  
21 show a statistically significant increase in the risk of heart attack or stroke at 200 mg/d.

22 Finally, Dr. Rymer cited Gislason, discussed above, and Brophy,<sup>6</sup> as support for  
23 causation at 200 mg/d. Brophy, as Gislason, evaluated the risk of heart attack in patients  
24 who had already had at least one heart attack. Brophy, however, did not find a  
25 statistically significant increased risk of heart attack at 200 mg/d, even in these high risk

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27 <sup>6</sup> James M. Brophy, The coronary risk of cyclo-oxygenase-2 inhibitors in patients with a  
28 previous myocardial infarction. Plaintiffs cited this study as being available at  
heart.bmj.com or at www.heartjnl.com.

1 patients. And while it did show a greater risk in the high risk population (although not a  
2 statistically significant risk), the higher risk found in Brophy and Gislason is contradicted  
3 by the results of at least nine other studies, including Dr. Doherty's "strongest evidence"  
4 of causation, the Andersohn heart study. Such data cannot reliably form the basis for  
5 rejecting the overwhelming pattern of evidence that fails to show any statistically  
6 significant risk at 200 mg/d.

### 7                   **3.     Extrapolation**

8           Dr. Doherty, and to some extent Dr. Rymer, also rely on studies of Celebrex 400  
9 mg/d to support their opinion of causation at 200 mg/d. Although Dr. Doherty  
10 acknowledges that dose matters with Celebrex, he simply takes the relative risk point  
11 estimate of APC for 400 mg/d and cuts it in half (ignoring the confidence interval) to  
12 support his opinion that Celebrex at 200 mg/d can cause a heart attack. Oct. 10 TR at 304.  
13 When the Court asked Dr. Doherty if there is anything in the scientific literature to  
14 support such primitive extrapolation, he failed to identify any scientific support for his  
15 method other than his own judgment. Id. at 342-43, 378-79. He also admitted that there is  
16 no way of knowing what the confidence interval is for 200 mg/d under his unique  
17 methodology. Id. at 340-41. Such an unscientific, untested methodology cannot support  
18 the proffered opinion of causation at 200 mg/d, especially where, as here, Dr. Doherty  
19 agrees with all the other experts that there is dose effect with Celebrex.

20           Plaintiffs' reliance on In re PPA Products Liab. Litig., 289 F.Supp.2d 1230 (W.D.  
21 Wa. 2003), to argue that causation at 200 mg/d can be inferred from the 400 mg/d data is  
22 misplaced. In the PPA multi-district litigation the issue was whether PPA, a drug used in  
23 cough and cold and appetite suppressant products, can cause strokes. Plaintiffs' experts'  
24 opinion that PPA can cause strokes in persons of all ages and genders was based primarily  
25 upon a study of women ages 18 to 49. Id. at 1235-36. While men were not excluded from  
26 the study, their participation was too low to draw any conclusions. Id. at 1236. The  
27 defendants argued that the evidence was therefore insufficient to support the plaintiffs'  
28 experts' opinions that PPA can cause strokes in persons of all ages and genders. Id. at

1 1244. The district court disagreed.

2 The court found that “it is scientifically acceptable to extrapolate the conclusions of  
3 the [study] to these sub-populations.” Id. at 1244. As to persons older than 49, the court  
4 noted that there are no known studies that suggest that drugs get safer as persons get older;  
5 thus, it made common scientific sense to extrapolate the results of the study to persons  
6 over 49. Id. Plaintiffs’ experts also attested to the “commonplace” practice of  
7 extrapolating between the genders based on “the historical exclusion of women from  
8 scientific studies.” Id.

9 The justification for extrapolating drug effects between biologically similar  
10 demographic groups, however, does not logically extend to the argument that all doses of  
11 a compound are harmful; accordingly, plaintiffs’ experts could not cite to a single piece of  
12 evidence that suggests that their experts’ extrapolation is scientifically valid. To the  
13 contrary, with nearly all compounds there is usually a threshold that must be met before  
14 there is any harm; for example, even water can be harmful if consumed at certain amounts  
15 even though there is no harm at smaller amounts. Dr. Doherty claimed that the threshold  
16 for Celebrex must be 50 mg/d because that is the dose that is effective for pain relief.  
17 That “theory,” however, is nothing more than Dr. Doherty’s wholly untested, unpublished,  
18 and non-peer reviewed justification for his reliance on the 400 mg/d data. Moreover, the  
19 great weight of the evidence does not support the extrapolation, that is, studies show that  
20 there is no statistically significant association between Celebrex 200 mg/d and the risk of  
21 strokes or heart attacks.

22 Instead of citing evidence that supports such extrapolation, plaintiffs complain that  
23 the evidence of harm at 200 mg/d does not exist because Pfizer did not initiate long term  
24 randomized trials at such dose. Such a trial, known as PRECISION, is now underway, but  
25 the results will not be available for some time. Plaintiffs cite no case, however, that  
26 suggests that they can satisfy their burden of proof based on a lack of evidence; plaintiffs  
27 filed these lawsuits and plaintiffs carry the burden of proving today based on currently  
28 available scientifically valid evidence that Celebrex can cause heart attacks or strokes at

1 200 mg/d.

2 Plaintiffs have not met their burden. In so finding, the Court is relying on the  
3 evidence presented by plaintiffs; it has not considered Pfizer's own meta-analyses. And  
4 the Court's ruling is not mandated by the lack of randomized clinical trials that show an  
5 association at 200 mg/d; plaintiffs could still meet their burden in the absence of such  
6 evidence. See Kennedy v. Collagen Corp., 161 F.3d 1226, 1228 (9th Cir. 1998).  
7 However, the opinion of Dr. Doherty and Dr. Rymer that Celebrex 200 mg/d increases the  
8 risk of heart attacks or strokes is not based on a scientific valid methodology; instead,  
9 these experts ignore the great weight of the observational studies that contradict their  
10 conclusion and instead rely on the handful that appear to support their litigation-created  
11 opinion. As the Court explained above, their reasons for doing so are not supported by  
12 scientifically valid reasons or methodology. In the words of the Supreme Court, the  
13 "analytical gap" between the data and these experts' conclusion is simply too great to  
14 make the opinion admissible. General Elect. Co. v. Joiner, 522 U.S. 136, 146 (1997).

15 **B. 400 mg/d**

16 Pfizer's motion to exclude expert testimony that Celebrex 400 mg/d is capable of  
17 causing heart attacks or strokes is defeated by APC, a large, long-term, randomized,  
18 placebo-controlled, double-blind, multi-center clinical trial that was halted after 33  
19 months because it demonstrated a statistically significant risk of heart attack, stroke, and  
20 heart failure at 400 mg/d (2.6 percent hazards ratio with a confidence interval of 1.1 to  
21 6.1) and 800 mg/d (3.4 percent hazards ratio with a confidence interval of 1.5 to 7.9).<sup>7</sup>  
22 The study, co-sponsored by the National Cancer Institute and Pfizer, was designed to  
23 compare Celebrex with placebo for the prevention of colorectal adenomas (polyps). The  
24 study included a "cardiovascular safety committee" that developed guidelines to evaluate  
25 cardiovascular safety. On December 16, 2004, on the basis of the results then available as

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27 <sup>7</sup> Scott D. Solomon, et al., Cardiovascular Risk Associated with Celecoxib in a Clinical  
28 Trial for Colorectal Adenoma Prevention, N. Engl. J. Med. 2005 Mar 17; 352(11): 1071-  
1080.

1 well as studies of Vioxx and Bextra, and on the recommendation of the safety committee,  
2 the APC steering committee stopped the trial. This randomized, placebo-controlled,  
3 double-blinded study with an independent committee evaluating cardiovascular endpoints  
4 is the “gold standard” of epidemiologic evidence and supports plaintiffs’ experts’  
5 testimony that Celebrex at 400 mg/d is capable of causing heart attacks or strokes.

6 Pfizer nonetheless contends that plaintiffs’ experts’ opinion must be excluded  
7 because (1) APC was stopped early, and (2) its results have not been replicated by two  
8 other randomized controlled trials that evaluated Celebrex 400 mg/d: ADAPT and  
9 PreSAP.

10 The Court is unconvinced that plaintiffs’ experts cannot base their opinions on APC  
11 because it was stopped early (after 33 months). The APC steering committee halted the  
12 trial because the evidence of harm was so significant. To exclude reliance on such studies  
13 under these circumstances would mean the more harmful the drug the more difficult it is  
14 to prove harm. While such studies must be closely scrutinized due to their early  
15 termination, Pfizer’s argument goes to the study’s weight; Pfizer has not shown that it is  
16 not scientifically valid for plaintiffs’ experts to rely on the results. Moreover, ADAPT  
17 and PreSAP, two studies upon which Pfizer relies, were also halted early because of the  
18 APC results.

19 The Court is also not persuaded that the failure of ADAPT and PreSAP to replicate  
20 APC’s results means plaintiffs’ expert opinion on 400 mg/d is inadmissible. ADAPT was  
21 a randomized, placebo-controlled clinical trial designed to evaluate naproxen and  
22 Celebrex 400 mg/d (200 mg twice daily) and the prevention of Alzheimer’s dementia.<sup>8</sup>  
23 ADAPT found a hazards ratio for Celebrex of 1.10 percent with a confidence interval of  
24 .67 to 1.79, that is, no statistically significant association. The study authors, however,  
25 cautioned that there are several limitations to their data. First, ADAPT was not designed

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26 <sup>8</sup> ADAPT Research Group, Cardiovascular and Cerebrovascular Events in the  
27 Randomized, Controlled Alzheimer’s Disease Anti-Inflammatory Prevention Trial  
28 (ADAPT), PLoS Clin Trials 2006; 1(7): e33.

1 to detect differences in cardiovascular and cerebrovascular risks and, unlike APC, it did  
2 not include a separate cardiovascular safety committee tasked solely with evaluating  
3 cardiovascular outcomes. Second, and, according to the authors, the largest limitation of  
4 the data is the small number of cardiovascular events. Third, an editorial comment  
5 accompanying the study suggests that because study participants eligible to join the trial  
6 were required to have a family history of Alzheimer's disease, it is possible the study  
7 participants' risk factors differed from the general population. The results of ADAPT  
8 need to weighed with the APC results, but ADAPT's conclusions do not make reliance on  
9 APC scientifically invalid.

10 The results of PreSAP, a randomized controlled study with fewer participants than  
11 ADAPT or APC, also did not replicate the APC results. PreSAP, as APC, was designed  
12 to evaluate Celebrex's effect on the occurrence of colorectal adenomas. Preliminary  
13 results from that study did not show a statistically significant increase in cv risk for  
14 patients taking Celebrex 400 mg/d, but did not exclude the possibility of a hazards ratio  
15 similar to that demonstrated by APC. In addition, PreSAP used the same independent  
16 cardiovascular safety committee as APC to assess the risk of Celebrex on adverse cv  
17 events. Accordingly, the data from both trials were synthesized to produce a combined  
18 estimate of risk of cardiovascular death, heart attack, stroke or heart failure of 1.9 with a  
19 confidence interval of 1.1 to 3.1; in other words, combining the raw data showed a  
20 statistically significant increase in risk.<sup>9</sup> The study authors combined APC 400 mg/d and  
21 800 mg/d with PreSAP 400 mg/d because the confidence intervals for 400 mg/d and 800  
22 mg/d substantially overlapped. While the weight to be given to this evidence can be  
23 argued, in light of this evidence, and the Kearney meta-analysis which found a relative  
24 risk greater than one with a confidence interval that barely crossed one, the Court cannot  
25 conclude that expert opinion that Celebrex 400 mg/d is capable of causing heart attacks

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26  
27 <sup>9</sup> Scott D. Solomon, et al., Effect of Celecoxib on Cardiovascular Events and Blood  
28 Pressure in Two Trials for the Prevention of Colorectal Adenomas, *Circulation*, 2006 Sep  
5; 114(10): 1028-35.

1 and strokes is scientifically invalid.

2 **C. Whether Celebrex Causes Heart Attacks or Strokes More Than Three**  
3 **Days After A Patient Stops Taking It**

4 Plaintiffs do not dispute that Celebrex is not capable of causing hearts attacks or  
5 strokes more than three days after a patient stops taking it and they have offered no expert  
6 opinion to the contrary. Accordingly, there is no proposed expert testimony on this issue  
7 for the Court to exclude.

8 **D. Remaining Issues**

9 **1. Strokes**

10 The issue as to whether Celebrex is capable of causing strokes is close. Plaintiffs  
11 rely on the testimony of Dr. Rymer, a neurologist and the Medical Director of the Saint  
12 Luke's Brain and Stroke Institute at Saint Luke's Hospital in Kansas City, Missouri. She  
13 testified that the mechanism of and risk factors for throembolic strokes (excluding  
14 cardiogenic embolism) and heart attacks are the same; thus, if Celebrex causes an  
15 increased risk in heart attacks it also increases the risk of strokes. Rymer Written Direct  
16 ¶ 11-13. Dr. Rymer's testimony is supported by the published literature as nearly all  
17 studies of COX-2 inhibitors and cv risk lump strokes together with heart attacks. For  
18 example, the Kearney meta-analysis of clinical trials identified the relative risk for  
19 "serious vascular events," defined as heart attack, stroke, or vascular death. Indeed, even  
20 Pfizer's expert, Dr. Packer, considers the risk of heart attacks and strokes together, and  
21 Pfizer does not dispute Dr. Rymer's testimony as to the similar mechanism of heart  
22 attacks and strokes.

23 Pfizer nonetheless asserts that Dr. Rymer's testimony is inadmissible because the  
24 randomized controlled trials and observational studies that do separately report strokes  
25 and heart attacks do not suggest an association between Celebrex at any dose and strokes.  
26 Dr. Rymer explains, however, that none of the randomized controlled studies was  
27 designed to look for stroke outcomes, and strokes occur far less often than heart attacks;  
28 the studies simply were not designed to find an association or not.



1 While there is some epidemiologic evidence to dispute her mechanism testimony,  
2 that is, evidence that suggests that even though heart attacks and certain strokes are caused  
3 by the same mechanism Celebrex does not cause both, there is also some evidence to  
4 support her testimony. On the current record the Court does not find that Dr. Rymer's  
5 testimony is scientifically invalid and inadmissible. See Daubert, 509 U.S. at 596  
6 ("Vigorous cross-examination, presentation of contrary evidence, and careful instruction  
7 on the burden of proof are the traditional and appropriate means of attacking shaky but  
8 admissible evidence.").

## 9 **2. Duration**

10 The Court also denies Pfizer's motion to exclude testimony that Celebrex is  
11 capable of causing heart attacks or strokes only after 33 months of continuous use.  
12 Because a statistically significant association did not appear in APC until after 33 months  
13 does not mean as a matter of scientific fact that none of the adverse cv events that  
14 occurred after a shorter duration were not caused by the patient's ingestion of Celebrex.

## 15 **3. Specific Causation**

16 Finally, Pfizer asks the Court to "exclude any opinion that Celebrex caused an  
17 individual plaintiff's heart attack or stroke absent a relative risk that exceeds 2.0." This is  
18 a question of specific causation as to particular plaintiffs; as the Court does not have  
19 before it evidence as to any specific plaintiff the Court declines to grant Pfizer's motion.

## 20 **II. Plaintiffs' Motion to Exclude**

21 Plaintiffs move to exclude the meta-analyses performed by Pfizer's experts.  
22 Plaintiffs' experts did not perform any of their own meta-analyses; instead, plaintiffs  
23 attack Pfizer's experts' methodologies. Plaintiffs' motion is denied. All of plaintiffs'  
24 arguments go to the weight a trier of fact gives to the meta-analyses. Plaintiffs have not  
25 shown that the methods employed by Pfizer's experts are not based on good science.

26 Plaintiffs also move to exclude Dr. Packer from testifying as to an alternative  
27 theory to the imbalance hypothesis. Dr. Packer's explanation, which accounts for the  
28 difference in outcomes between Vioxx and Celebrex, is based on increased blood

1 pressure, a theory actually supported by plaintiffs' expert Dr. Rymer. In any event, Dr.  
2 Packer's testimony satisfies Daubert.

### 3 CONCLUSION

4 In Daubert, the Supreme Court held that federal judges perform a gatekeeping role,  
5 509 U.S. at 597, and "to do so they must satisfy themselves that scientific evidence meets  
6 a certain standard of reliability before it is admitted." Daubert II, 43 F.3d at 1316.  
7 Plaintiffs' expert testimony that Celebrex 200 mg/d can cause heart attacks or strokes does  
8 not meet that standard. Dr. Doherty, a clinical physician with no relevant research  
9 experience and who developed his opinion for the purpose of testifying, bases his opinion  
10 on a study that he fundamentally misunderstood, is counter to the great weight of the  
11 evidence, and, by his own admission, does not make biological sense. The Court cannot  
12 find that his opinion is good science. Dr. Rymer's 200 mg/d opinion is also not good  
13 science. She ignores all the evidence that contradicts her litigation-created conclusion and  
14 instead bases her opinion on the same cherry-picked study as Dr. Doherty, even though  
15 that study suffers from the exact same limitations that caused her to reject other studies  
16 that do not support her conclusion. She also relies on an unpublished, non-peer reviewed  
17 study that does not disclose its design or confidence intervals. If the Court's gatekeeping  
18 function means anything, it must mean that these unreliable opinions are not admissible to  
19 prove general causation at 200 mg/d.

20 In all other respects, and for the reasons explained above, the parties' motions are  
21 denied.

22 **IT IS SO ORDERED.**

23 Dated: November 19, 2007

24 /s/  
HONORABLE CHARLES R. BREYER  
UNITED STATES DISTRICT JUDGE